PATENT SPECIFICATION

NO DRAWINGS

Inventors: DAVID NEVILLE KIRK and VLADIMIR PETROW

852,847

Date of filing Complete Specification: Feb. 24, 1959.

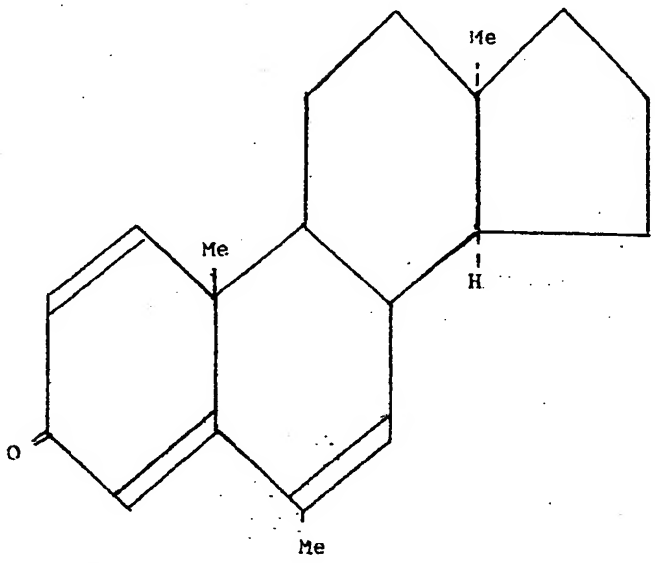
Application Date: March 4, 1958. *No. 6955/58.*

PATENTS ACT, 1949

SPECIFICATION NO. 852,847

In accordance with the Decision of the Assistant Comptroller, acting for the Comptroller-General, dated the 20th day of November, 1961, this Specification has been amended under Section 14 in the following manner:-

Page 1, *for* the formula following line 23, and Page 9, *for* the formula following line 5, substitute:-



Page 1, line 25, *delete*
line 26, *delete* "group"

Page 2, lines 125 and 126, *delete*

Page 3, lines 13 and 14, *delete*

Page 9, lines 7 and 8, *delete*
lines 63 and 64, *delete*
line 65, *for* "34" *read* "33"
line 67, *for* "35" *read* "34"
line 69, *for* "36" *read* "35"
line 71, *for* "37" *read* "36"
line 73, *for* "38" *read* "37"
line 75, *for* "39" *read* "38"
line 77, *for* "40" *read* "39"
line 79, *for* "41" *read* "40"
lines 81 and 82, *delete*
line 83, *for* "43" *read* "41"

THE PATENT OFFICE,
26th January, 1962.

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Index at acceptance:—**Classes 2(3)**, U2, U4(A1 : A2 : B1 : B2 : C1 : C2 : C3 : C4 : C5 : C9 : C10 : D : X), U5); **and 81(1)**, B(1Z : 2Z).

International Classification:—**A61k. C07c.**

COMPLETE SPECIFICATION

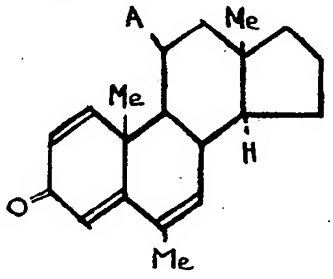
Improvements in or relating to 6-Methyl Steroid Compounds

We, THE BRITISH DRUG HOUSES LIMITED, a British Company, of 16—34 Graham Street, City Road, London, N.1, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is for improvements in or relating to 6-methyl steroid compounds and has particular reference to the 1-dehydro derivatives of certain unsaturated steroidal 6-methyl-3-ones.

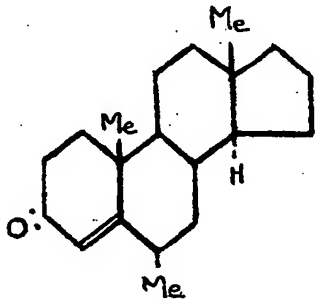
It is an object of the present invention to provide a process for the conversion of 3 - oxo - Δ^4 - 6 - methyl and 3 - oxo - $\Delta^{4:6}$ - 6 - methyl steroidal derivatives into the corresponding 1 - dehydro - derivatives which are a new class of compounds often possessing high biological activity.

The present invention provides 3 - oxo - $\Delta^{1:4:6}$ - 6 methyl steroids having, apart from substituents at the 16- and 17-positions, the general formula



where A is hydrogen or a keto or hydroxyl group which derivatives are of value on account of their biological properties or as intermediates in the preparation of compounds with useful biological properties as herein indicated or as is apparent to those skilled in the art.

According to the present invention there is provided a process for the preparation of 3 - oxo - $\Delta^{1:4}$ - 6 - methyl and 3 - oxo - $\Delta^{1:4:6}$ - 6 - methyl steroids which process comprises reacting the corresponding 3 - oxo - Δ^4 - 6 - methyl or 3 - oxo - $\Delta^{4:6}$ - 6 - methyl steroid including the structure



(II)

(with or without a double bond at the 6:7 position) with 2:3 - dicyano - *p* - benzoquinone, which may be additionally substituted with one or two chlorine atoms, in a solvent. Preferably 2:3 - dicyano - 5:6 - dichloro - 1:4 - benzoquinone is employed.

The choice of solvent is not critical providing both the steroid and quinone are soluble and stable therein. Benzene, dioxan, propyl acetate and acetic acid are preferred. Other solvents that may be employed include chlorobenzene, diethyleneglycol diethyl ether, phenetole, dimethylformamide or nitrobenzene. The dehydrogenation reaction is preferably carried out at an elevated temperature and conveniently between 80° C. and 110° C. Theoretically the reaction is best performed under nitrogen, but this precaution has little practical significance in the majority of cases herein. The rate of dehydrogenation may be increased by addition of a catalytic quantity

of a proton donor and in particular by the addition of a catalytic quantity of *p* - nitrophenol. Completion of the reaction is generally indicated by discharge of the colour of the quinone and/or by the fact that further quantities of the hydroquinone derivatives are no longer deposited from the hot reaction liquors. Alternatively, completion of the reaction may be determined by estimating the quantity of quinone present in the reaction liquors by standard methods well known to those skilled in the art.

The 1 - dehydro - steroidal derivative is isolated from the reaction liquors by any convenient procedure. Thus the reaction liquors may be filtered to remove the sparingly soluble hydroquinone, extracted with aqueous alkali to remove phenolic products, evaporated to dryness, under reduced pressure if desired, and the residual solids crystallised in the usual way. Other methods will be apparent to those skilled in the art.

The process of the invention is of wide applicability and may, in general, be applied to 3 - oxo - Δ^4 - 6 - methyl and 3 - oxo - $\Delta^{1:6}$ - 6 - methyl derivatives of androstane, pregnane, cholestane and spirostane containing additional substituents which do not interfere with the process of the invention as hereinunder indicated.

Oxo groups, and in particular oxo groups in positions C-11, 17 and 20 (including 20 - oxo - 16 - ene).

Hydroxy, alkoxy and acyloxy groups, and in particular hydroxy, alkoxy and acyloxy groups in positions C-6, 11, 16, 17, 20 and 21.

Fluorine atoms, and in particular fluorine atoms in position C-9.

Alkyl groups, and in particular alkyl groups containing up to 5 carbon atoms in positions C-2, 4, 16 and 17.

Vinyl groups and in particular vinyl groups at position C-17.

Ethynyl and substituted ethynyl groups containing up to 4 carbon atoms, and in particular such groups at position C-17.

The invention also provides the following new steroidal 6 - methyl - 1:4 - dien - 3 - ones and 6 - methyl - 1:4:6 - trien - 3 - ones which are of value in steroid technology, in the furtherance of steroidal research and in the application of steroidal materials to veterinary or medical practice, whether as tablets, elixirs, injections, implants, or other types of pharmaceutical preparation well known to those skilled in the art.

Cholestane series

6α - Methylcholesta - 1:4 - dien - 3 - one and 6 - methylcholesta - 1:4:6 - trien - 3 - one which are of value for the reduction of blood cholesterol levels.

Spirostane series

6α - Methyl - 25D - spirosta - 1:4 - dien - 3 - one, 6 - methyl - 25D - spirosta - 1:4:6 - trien - 3 - one and 6 - hydroxy - 6 - methyl - 25D - spirosta - 1:4 - dien - 3 - one which are of value as intemediates in the preparation of 6 - methylated aromatic steroid hormones into which intermediates they may be converted by reaction in solution in acetic anhydride with toluene - *p* - sulphonic acid.

Androstane series

17β - Hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one

17β - Hydroxy - 6β - methylandrosta - 1:4 - dien - 3 - one

17β - Hydroxy - 6 - methylandrosta - 1:4:6 - trien - 3 - one

6α - Methylandrosta - 1:4 - diene - 3:17 - dione

6β - Methylandrosta - 1:4 - diene - 3:17 - dione

6 - Methylandrosta - 1:4:6: - triene - 3:17 - dione

17β - Hydroxy - 6α:17α - dimethylandrosta - 1:4 - dien - 3 - one

17β - Hydroxy - 6β:17α - dimethylandrosta - 1:4 - dien - 3 - one

17β - Hydroxy - 6:17α - dimethylandrosta - 1:4:6 - trien - 3 - one

17α - Ethynyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one

17α - Ethyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one

17α - Vinyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one

17α - (But - 1 - ynyl) - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one

17α - Ethynyl - 17β - hydroxy - 6 - methylandrosta - 1:4:6 - trien - 3 - one

17β - Acetoxy - 4:6α - dimethylandrosta - 1:4 - dien - 3- one

17β - Acetoxy - 2:6α - dimethylandrosta - 1:4 - dien - 3 - one

9α - Fluoro - 11β:17β - dihydroxy - 6α:17α - dimethylandrosta - 1:4 - dien - 3 - one

17β - Hydroxy - 6α - methyl - 17α - (prop - 1 - ynyl) - androsta - 1:4 - dien - 3 - one

which are of value as intermediates in the preparation of 6-methylated aromatic steroidal hormones, into which they may be converted by reaction in solution in acetic anhydride with toluene - *p* - sulphonic acid, as intermediates in the preparation of biologically active compounds and in some cases on account of their biological properties.

Pregnane series

6α - Methylpregna - 1:4 - diene - 3:20 - dione

6 - Methylpregna - 1:4:6 - triene - 3:20 - dione

17α - Hydroxy - 6α methylpregna - 1:4 - diene - 3:20 - dione

17α - Hexanoyloxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione

11α - Hydroxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione

11 - Oxo - 6α - methylpregna - 1:4 - diene - 3:20 - dione

6α:16α - Dimethylpregna - 1:4 - diene - 3:20 - dione
6α - Methylpregna - 1:4:16 - triene - 3:20 - dione
6α - Methyl - 16α:17α - *iso*propylidenedioxy-pregna - 1:4 - diene - 3:20 - dione
20β - Hydroxy - 6α - methylpregna - 1:4 - dien - 3 - one
20:20 - Bisethylenedioxy - 6α - methyl-pregna - 1:4 - dien - 3 - one
Ethyl 6α - methyl - 3 - oxopregna - 1:4:17 (20) - trien - 21 - oate
17α - Acetoxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione

which are of value as intermediates in the preparation of compounds with valuable biological properties such as progestational properties or properties associated with the adreno-cortical hormones or as intermediates in the preparation of compounds with useful biological properties. Thus, for example, 17α:21 - dihydroxy - 6α - methylpregna - 1:4 - diene - 3:11:20 - trione and its acetate and 11β:17α:21 - trihydroxy - 6α - methyl-pregna - 1:4 - diene - 3:20 - trione and its acetate are of value on account of their hydrocortisone-like anti-inflammatory properties.

Following is a description by way of example of methods of carrying the invention into effect.

EXAMPLE 1

6α - Methylpregna - 1:4 - diene - 3:20 - dione

6α - Methylprogesterone (650 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (500 mg.) in dry benzene (30 ml.) were boiled under reflux for 12 hours. The solids were removed by filtration, and the filtrate diluted with ether and washed with 4% aqueous sodium hydroxide, then with water, dried (Na_2SO_4), stirred with decolourising charcoal, filtered and the solvent evaporated. Crystallisation from hexane gave 6α - *methylpregna - 1:4 - diene - 3:20 - dione*, prisms, m.p. 140 to 141° C., $[\alpha]_D^{22}+11°$ (*c*, 0.22 in chloroform); λ_{max} 245 mμ (15,400) in ethanol λ_{max} 1697, 1655, 1616, 1602 $cm.^{-1}$ (in chloroform).

EXAMPLE 2

6 - Methylpregna - 1:4:6 - triene - 3:20 - dione

6 - Methylpregna - 4:6 - diene - 3:20 - dione (200 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (200 mg.) in dry benzene (10 ml.) were heated under reflux for 7 hours. The product was isolated as in the previous example. 6 - *Methylpregna - 1:4:6 - triene - 3:20 - dione* separated from acetone/hexane (1:6) in rods, m.p. 168° C., $[\alpha]_D+100°$ (*c*, 0.25 in chloroform), λ_{max} 228 mμ (12,240) 303 mμ (10,860) $\lambda_{inflex.}$ 251 mμ (8,280) in ethanol.

EXAMPLE 3

6 - Methylandrosta - 1:4:6 - triene - 3:17 - dione

6 - Methylandrosta - 4:6 - diene - 3:17 - dione (60 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (50 mg.) in dry benzene (4 ml.) were heated under reflux for 12 hours, then the product was isolated as in previous examples. 6 - Methylandrosta - 1:4:6 - triene - 3:17 - dione formed prisms, [from acetone/hexane, (1:5)] m.p. 219 to 221° C., $[\alpha]_D^{22}+84°$ (*c*, 0.21 in chloroform), λ_{max} 227 mμ (12,720), 301 mμ (11,720) λ_{inflex} 250 mμ (9,050) in ethanol.

EXAMPLE 4

17β - Hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one

6α - Methyltestosterone (120 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (120 mg.) in dry benzene (6 ml.) were heated under reflux for 16 hours, and the product isolated as in previous examples. 17β - Hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one separated from ether/hexane (1:4) in prisms, m.p. 136 to 139° C., $[\alpha]_D^{21}+2°$ (*c*, 0.09 in chloroform) $\lambda_{max.}$ 244 mμ (13,270) in ethanol.

EXAMPLE 5

17β - Hydroxy - 6β - methylandrosta - 1:4 - diene - 3 - one

6β - Methyltestosterone, treated as described for the 6α - methyl isomer, gave 17β - hydroxy - 6β - methylandrosta - 1:4 - dien - 3 - one, prisms from ether, m.p. 188 to 190° C., λ_{max} 245 mμ (14,070) in ethanol.

EXAMPLE 6

17β - Hydroxy - 6β:17α - dimethylandrosta - 1:4 - dien - 3 - one

6β:17α - Dimethyltestosterone (100 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (100 mg.) in dry benzene (4 ml.) were heated under reflux for 7 hours, when the product was isolated as in previous examples. 17β - *Hydroxy - 6β:17α - dimethylandrosta - 1:4 - dien - 3 - one* separated from ether/hexane (1:6) in needles, $[\alpha]_D^{24}-17°$ (*c*, 0.23 in chloroform), m.p. 118 to 120° C., $\lambda_{max.}$ 245 mμ (14.480).

EXAMPLE 7

Purified dioxan (5 ml.) was substituted for benzene in the previous Example, with similar results.

EXAMPLE 8

n - Propyl acetate (5 ml.) was substituted for benzene in Example 1 with similar results.

EXAMPLE 9

Acetic acid (5 ml.) was substituted for benzene in Example 1 with similar results.

EXAMPLE 10

6α - Methylpregna - 1:4 - diene - 3:20 - dione

6α - Methylprogesterone (100 mg.), 2:3 - dichloro - 5:6 - dicyanobenzoquinone (90 mg.) and *p* - nitrophenol (10 mg.) in dry benzene were heated under reflux for 6 hours and the

product isolated as in Example 1. 6α - Methylpregna - 1:4 - diene - 3:20 - dione was obtained, m.p. and mixed m.p. 139 to 141° C. with the sample obtained in Example 1, $\lambda_{max.}$ 245 mμ (15,450) in ethanol.

EXAMPLE 11

2:3 - Dicyanobenzoquinone was substituted for the dichlorodicyanobenzoquinone in the previous example, and the mixture heated under reflux for 24 hours. 6α - *Methylpregna* - 1:4 - *diene* - 3:20 - *dione*, m.p. 139 to 140° C., $\lambda_{max.}$ 245 mμ (15,320) in ethanol was obtained.

EXAMPLE 12

17α - *Hydroxy* - 6α - *methylpregna* - 1:4 - *diene* - 3:20 - *dione*

17α - Hydroxy - 6α - methylprogesterone (200 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (200 mg.) in dry benzene (4 ml.) were heated under reflux for 7 hours, and the product isolated as in Example 1. 17α - Hydroxy - 6α - *methylpregna* - 1:4 - *diene* - 3:20 - *dione* separated from acetone/hexane (1:4) in prisms, m.p. 235 to 237° C., $[\alpha]_D^{28}$ +12° (*c*, 0.29 in chloroform), $\lambda_{max.}$ 244.5 mμ (14,700) in ethanol.

EXAMPLE 13

6α:16α - *Dimethylpregna* - 1:4 - *diene* - 3:20 - *dione*

6α:16α - Dimethylprogesterone (100 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (80 mg.) in dry benzene (8 ml.) were heated under reflux for 22 hours and the product isolated as in Example 1. 6α:16α - *Dimethylpregna* - 1:4 - *diene* - 3:20 - *dione* crystallised from acetone/hexane (1:3) in prisms, m.p. 132 to 134° C., $\lambda_{max.}$ 245 mμ (13,900) in ethanol.

EXAMPLE 14

6α - *Methylcholesta* - 1:4 - *dien* - 3 - *one*

6α - Methylcholest - 4 - en - 3 - one (150 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (120 mg.) in dry benzene (8 ml.) were heated under reflux for 18 hours, then the product was isolated as in Example 1. 6α - *Methylcholesta* - 1:4 - *dien* - 3 - *one* was obtained as a gum, $[\alpha]_D^{25}$ +21° (*c*, 0.15 in chloroform) $\lambda_{max.}$ 245 mμ (13,700) in ethanol.

EXAMPLE 15

6 - *Methylcholesta* - 1:4:6 - *trien* - 3 - *one*

6 - Methylcholesta - 4:6 - dien - 3 - one (250 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (200 mg.) in dry benzene (20 ml.) were heated under reflux for 10½ hours, then the product was isolated as in Example 1. 6 - *Methylcholesta* - 1:4:6 - *trien* - 3 - *one* crystallised from aqueous ethanol in prisms, m.p. 80 to 81° C. $\lambda_{max.}$ 229 mμ (11,440), 303 mμ (9,290) $\lambda_{inflex.}$ 250 mμ (8,460).

EXAMPLE 16

6α - *Methyl* - 25D - *spirosta* - 1:4 - *dien* - 3 - *one*

6α - Methyl - 25D - spirost - 4 - en - 3 - one (50 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (45 mg.) in dry benzene (4 ml.) were heated under reflux for 35 hours, and the product isolated as in Example 1. 6α - *Methyl* - 25D - *spirosta* - 1:4 - *dien* - 3 - *one* separated from methylene chloride/methanol (1:4) in needles, m.p. 237 to 239° C., $\lambda_{max.}$ 244 mμ (15,330), $[\alpha]_D^{29}$ −34° (*c*, 0.19 in chloroform).

EXAMPLE 17

6 - *Methyl* - 25D - *spirosta* - 1:4:6 - *trien* - 3 - *one*

6 - Methyl - 25D - spirosta - 4:6 - dien - 3 - one (210 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (160 mg.) in dry benzene (20 ml.) were heated under reflux for 11 hours, then the product was isolated as in Example 1. 6 - *Methyl* - 25D - *spirosta* - 1:4:6 - *trien* - 3 - *one* formed needles from methylene chloride/methanol (1:3), m.p. 253 to 255° C., $\lambda_{max.}$ 228 mμ (13,110), 303 mμ (11,252), $\lambda_{inflex.}$ 250 mμ (9,260).

EXAMPLE 18

17β - *Hydroxy* - 6 - *methylandrosta* - 1:4:6 - *trien* - 3 - *one*

17β - Hydroxy - 6 - methylandrosta - 4:6 - dien - 3 - one (100 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (85 mg.) in dry benzene (4 ml.) were heated under reflux for 13 hours, then the product was isolated as in Example 1. 17β - *Hydroxy* - 6 - *methylandrosta* - 1:4:6 - *trien* - 3 - *one* separated from ether/hexane (1:4) in prisms, m.p. 169 to 170° C., $\lambda_{max.}$ 228 mμ (11,470), 251 mμ (8,020), 302.5 mμ (10,520).

EXAMPLE 19

6α - *Methylandrosta* - 1:4 - *diene* - 3:17 - *dione*

6α - Methylandrost - 4 - ene - 3:17 - dione (120 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (100 mg.) in dry benzene (10 ml.) were heated under reflux for 24 hours, then the product was isolated as in Example 1. 6α - *Methylandrosta* - 1:4 - *diene* - 3:17 - *dione* separated from acetone/hexane (1:6) in prisms, m.p. 210 to 212° C., $\lambda_{max.}$ 243 mμ (14,540), $[\alpha]_D^{25}$ +103 (*c*, 0.28 in chloroform).

EXAMPLE 20

6β - *Methylandrosta* - 1:4 - *dien* - 3:17 - *dione*

6β - Methylandrost - 4 - ene - 3:17 - dione (80 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (70 mg.) in dry benzene (7 ml.) were heated under reflux for 13 hours, then the product was isolated as in Example 1. 6β - *Methylandrost* - 4 - *ene* - 3:17 - *dione* crystallised from ether-hexane (1:5) in needles, m.p. 176 to 178° C., $\lambda_{max.}$ 243 mμ (14,000), $[\alpha]_D^{25}$ +102 (*c*, 0.19 in chloroform).

EXAMPLE 21

2:3 - Dicyanobenzoquinone (50 mg.) was substituted for the dichloro - dicyanobenzoquinone in Example 3, and heating was continued for 20 hours with similar results.

EXAMPLE 22

17β - Hydroxy - 6α: 17α - Dimethylandrosta - 1:4 - dien - 3 - one

17β - Hydroxy - 6α: 17α - dimethylandrost - 4 - en - 3 - one (60 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (50 mg.) in dry benzene (4 ml.) were heated under reflux for 10 hours, then the product was extracted as in Example 1. *17β - Hydroxy - 6α: 17α - dimethylandrosta - 1:4 - dien - 3 - one* crystallised from ether/hexane (1:8) in rectangular prisms, m.p. 143 to 144° C., $\lambda_{max.}$ 244 mμ (14,080) in ethanol.

EXAMPLE 23

17β - Hydroxy - 6: 17α - dimethylandrosta - 1:4:6 - trien - 3 - one

17β - Hydroxy - 6: 17α - dimethylandrosta - 4:6 - dien - 3 - one (110 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (90 mg.) in dry benzene (10 ml.) were heated under reflux for 20 hours, and the product isolated as in Example 1. *17β - Hydroxy - 6:17α - dimethylandrosta - 1:4:6 - trien - 3 - one* separated from ether/hexane (1:3) in needles, m.p. 148 to 149° C., $\lambda_{max.}$ 229 mμ (12,780), 250 mμ (8,840), 303 mμ (11,215) in ethanol.

EXAMPLE 24

17α - Ethynyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one

6α - Methylethisterone (150 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (170 mg.) and *p* - nitrophenol (15 mg.) in dry benzene (8 ml.) were heated under reflux for 18 hours, and the product isolated as in Example 1. *17α - Ethynyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one* separated from ether/hexane (1:1) in prisms, m.p. 140 to 142° C., $\lambda_{max.}$ 244 mμ (13,730) in ethanol.

EXAMPLE 25

17α - Vinyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one

17α - Vinyl - 17β - hydroxy - 6α - methylandrost - 4 - en - 3 - one (0.5 g.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (0.5 g.) in dry benzene (10 ml.) were heated under reflux for 26 hours. *17α - Vinyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one,* isolated as in Example 1, crystallised from acetone/hexane (1:4) in prisms, m.p. 187 to 189° C., $[\alpha]_D^{20}$ + 3° (*c*, 0.18 in chloroform) $\lambda_{max.}$ 244.5 mμ (14,760) in ethanol.

EXAMPLE 26

17α - (But - 1 - ynyl) - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one

17α - (But - 1 - ynyl) - 17β - hydroxy - 6α - methylandrost - 4 - en - 3 - one (200 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (160 mg.) in dry benzene (15 ml.) were heated under reflux for 20 hours and the product isolated as in Example 1. *17α - (But - 1 - ynyl) - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one* crystallised from ether/hexane (1:4) in needles, m.p. 133 to 136° C., $\lambda_{max.}$ 245 mμ (13,370) in ethanol.

EXAMPLE 27

17α:21 - Dihydroxy - 6α - methylpregna - 1:4 - diene - 3:11:20 - trione

6α - Methylcortisone (200 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (200 mg.) in purified dioxan (5 ml.) were heated under reflux until no further deposition of 2:3 - dichloro - 5:6 - dicyanohydroquinone (glistening plates) was observed (8 hours). The mixture was diluted with chloroform, the solids removed by filtration, and the solution washed with 5% sodium hydroxide solution saturated with sodium chloride until no more colour was removed in the aqueous phase. The chloroform was then washed with saturated sodium chloride solution, dried (Na_2SO_4) and evaporated. Purification from ethyl acetate/hexane (1:2) gave *17α:21 - dihydroxy - 6α - methylpregna - 1:4 - diene - 3:11:20 - trione* in prisms, m.p. 231 to 234° C., $\lambda_{max.}$ 238.5 mμ (14,130) in ethanol.

EXAMPLE 28

21 - Acetoxy - 17α - hydroxy - 6α - methylpregna - 1:4 - diene - 3:11:20 - trione

6α - Methylcortisone acetate (60 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (50 mg.) in purified dioxan (3 ml.) were heated under reflux for 10 hours, and the product isolated as in Example 27. *21 - Acetoxy - 17α - hydroxy - 6α - methylpregna - 1:4 - diene - 3:11:20 - trione* was identified by its ultra-violet absorption spectrum, ($\lambda_{max.}$ 238.5 mμ [ε = 13,740] in ethanol) and infrared absorption spectrum ($\upsilon_{max.}$ 1664, 1622, 1603 $cm.^{-1}$ in chloroform).

EXAMPLE 29

11β:17α:21 - Trihydroxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione

6α - Methyl - hydrocortisone (100 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (90 mg.) in anhydrous dioxan (5 ml.) were heated under reflux for 18 hours. Isolation as described under Example 27, and purification from aqueous acetone, gave *11β:17α:21 - trihydroxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione,* m.p. 204 to 208° C., $[\alpha]_D^{22}$ + 98° (*c*, 0.21 in dioxan), $\lambda_{max.}$ 243 mμ (ε 14,600) (in ethanol).

EXAMPLE 30

21 - Acetoxy - 11β:17α - dihydroxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione

21 - Acetoxy - 11β:17α - dihydroxy - 6α - methylpregn - 4 - ene - 3:20 - dione (60 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (50 mg.) were heated in purified dioxan (4 ml.) under reflux for 12 hours. The product, isolated as in Example 27 was purified from aqueous acetone to give *21 - acetoxy - 11β:17α - dihydroxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione,* m.p. 203 to 206° C., $[\alpha]_D^{22}$ + 103° (*c*, 0.12 in dioxan), $\lambda_{max.}$ 243.5 mμ (ε = 14,750) in ethanol.

EXAMPLE 31

17α - *Ethyl* - 17β - *hydroxy* - 6α - *methyl-androsta* - 1:4 - *diene* - 3 - *one*

17α - Ethyl - 17β - hydroxy - 6α - methyl-androst - 4 - en - 3 - one (270 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (270 mg.) and *p* - nitrophenol (30 mg.) in dry benzene (4 ml.) were heated under reflux for 8½ hours and the product isolated as in Example 1. 17α - *Ethyl* - 17β - *hydroxy* - 6α - *methyl-androsta* - 1:4 - *dien* - 3 - *one* was obtained as a gum, $\lambda_{max.}$ 245 mμ (12,400) in ethanol.

EXAMPLE 32

6α - *Methylpregna* - 1:4:16 - *triene* - 3:20 - *dione*

6α - Methylpregna - 4:16 - diene - 3:20 - dione (150 mg.), 2:3 - dichloro - 5:6 - dicyanobenzoquinone (150 mg.) and *p* - nitrophenol (15 mg.) in dry benzene (5 ml.) were heated under reflux for 7 hours and the product isolated as in Example 1, and purified from ether/hexane (1:6). 6α - *Methylpregna* - 1:4:16 - *triene* - 3:20 - *dione* formed needles, m.p. 198 to 199° C., $\lambda_{max.}$ 241 mμ (22,710) in ethanol, $\nu_{max.}$ 1657, 1616, 1600, 1586 cm.$^{-1}$ in chloroform.

EXAMPLE 33

17α - *Ethynyl* - 17β - *hydroxy* - 6 - *methyl-androsta* - 1:4:6 - *trien* - 3 - *one*

17α - Ethynyl - 17β - hydroxy - 6 - methyl-androsta - 4:6 - dien - 3 - one (m.p. 202 to 204° C.) (840 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (840 mg.) in dry benzene (12 ml.) were heated under reflux for 3 hours and the product isolated as in Example 1. 17α - *Ethynyl* - 17β - *hydroxy* - 6 - *methyl-androsta* - 1:4:6 - *trien* - 3 - *one crystallised* from acetone/hexane (1:6) in prisms, m.p. 148 to 150° C., $\lambda_{max.}$ 228 mμ (12,680), 302.5 mμ (11.080), $\lambda_{inflex.}$ 250 mμ (8,760) in ethanol.

EXAMPLE 34

17β - *Acetoxy* - 4:6α - *dimethylandrosta* - 1:4 - *dien* - 3 - *one*

17β - Acetoxy - 4:6α - dimethylandrost - 4 - en - 3 - one was prepared as follows:

6α - Methyltestosterone (6 g.), thiophenol (4 ml.), formaldehyde (40% aqueous solution; 3.3 ml.), triethylamine (4 ml.) and ethanol (10 ml.) were heated under reflux for 60 hours, then the mixture was poured into water containing potassium hydroxide (6 g.). The product was isolated with ether and purified by chromatography on alumina to give 6α - *methyl* - 4 - *phenylthiomethyltestosterone* m.p. 102 to 105° C. $[\alpha]_D^{22}$ −45° (*c*, 1.016 in chloroform).

The foregoing compound (2 g.) was treated with acetic anhydride (6 ml.) and pyridine (5 ml.) for ½ hour at 80° C. then poured into water. The precipitate was collected and dried, then dissolved in acetone (30 ml.) and added to a mixture of Raney nickel (30 ml. settled sludge) and acetone (150 ml.) which had been previously heated under reflux for ½ hour. Heating was continued for 4½ hours then the nickel was removed by filtration and the filtrate evaporated to dryness. Purification of the residue from methanol gave 17β - *acetoxy* - 4:6α - *dimethylandrost* - 4 - *en* - 3 - *one*, m.p. 154 to 156° C. $\lambda_{max.}$ 250 mμ (14,730) in ethanol.

17β - Acetoxy - 4:6α - dimethylandrost - 4 - en - 3 - one (460 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (400 mg.) in dry benzene (10 ml.) were heated under reflux for 24 hours, and the product was isolated as in Example 1. 17β - *Acetoxy* - 4:6α - *dimethylandrosta* - 1:4 - *dien* - 3 - *one* crystallised from methanol in prisms, m.p. 138 to 140° C., $\lambda_{max.}$ 244 mμ (13,295) in ethanol, $\nu_{max.}$ 1725, 1660, 1622, 1592 and 1403 cm.$^{-1}$ in "Nujol", $[\alpha]_D^{21}$ −11° (*c*, 0.57 in chloroform).

EXAMPLE 35

17β - *Acetoxy* - 2:6α - *dimethylandrosta* - 1:4 - *dien* - 3 - *one*

17β - Acetoxy - 2α:6α - dimethylandrost - 4 - en - 3 - one was prepared as follows:

6α - Methyltestosterone (5 g.), ethyl oxalate (8 ml.), sodium hydride (2 g.) and dry benzene (120 ml.) were stirred for 24 hours, under nitrogen, then hexane (150 ml.) was added and the solids collected on a filter and dried. The product was treated with methyl iodide (10 ml.), anhydrous potassium carbonate (6 g.) and redistilled dimethylformamide (100 ml.) at 100° C., for 18 hours, poured into water and the product isolated with ether.

After evaporation of the ether, the residue was treated with a solution of sodium (1 g.) in methanol (125 ml.) for 18 hours at 20 to 25° C. The solution was poured into water, the product again isolated with ether, and the residue remaining after evaporation of the ether was acetylated with acetic anhydride (15 ml.) and pyridine (10 ml.) at 100° C. for ½ hour. Chromatographic purification of the product on alumina (100 g.) and crystallisation from hexane gave 17β - *acetoxy* - 2α:6α - *dimethylandrost* - 4 - *en* - 3 - *one* in prisms, m.p. 122 to 123° C. or 144 to 145° C., $[\alpha]_D^{21}$ + 78° (*c*, 0.98 in chloroform).

17β - Acetoxy - 2α:6α - dimethylandrost - 4- en - 3 - one (40 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (35 mg.) in dry benzene (2 ml.) were heated under reflux for 30 hours, and the product was isolated as in Example 1. 17β - *Acetoxy* - 2:6α - *dimethylandrosta* - 1:4 - *dien* - 3 - *one* was identified by its ultra-violet absorption [$\lambda_{max.}$ 244 (14,100) in ethanol] and infra-red absorption ($\nu_{max.}$ 1728, 1662, 1620 and 1402 cm.$^{-1}$ in "Nujol").

EXAMPLE 36

6ξ - *Hydroxy* - 6ξ - *methyl* - 25D - *spirosta* - 1:4 - *dien* - 3 - *one*

6ξ - Hydroxy - 6ξ - methyl - 25D - spirost - 4 - en - 3 - one was prepared as follows:—

3β - Acetoxy - 5α:6α - epoxy - 5α:25D -

spirostane (11.8 g.) in acetone (400 ml.) was heated under reflux for 30 minutes with periodic acid (2.85 g.) in water (30 ml.). The solution was filtered and poured into water. The precipitate was collected and crystallised from methanol to give 3β - *acetoxy* - 5α:25D - *spirostane* - 5α:6β - *diol*, needles, m.p. 286 to 288° C., $[\alpha]_D^{23} - 98°$.

3β - Acetoxy - 5α:25D - spirostane - 5α:6β - diol (7 g.) dissolved in pyridine (70 ml.) was oxidised with chromium dioxide (7 g.) in pyridine (70 ml.) for 48 hours at room temperature. The product was isolated with hot benzene. Crystallisation from chloroform/methanol (1:3) gave 3β - *acetoxy* - 5 - *hydroxy* - 5α:25D - *spirostan* - 6 - *one*, plates, m.p. 273 to 275° C., $[\alpha]_D^{23} - 127°$ (*c*, 0.886).

3β - Acetoxy - 5 - hydroxy - 5α:25D - spirostan - 6 - one in tetrahydrofuran (200 ml.) was added to methylmagnesium iodide solution, prepared from magnesium (2 g.) and methyl iodide (12 g.) in ether (200 ml.), and heated under reflux for 3 hours. Ammonium chloride solution was added and the product filtered off and crystallised from methanol to give 3β:5:6 - *trihydroxy* - 6ξ - *methyl* - 5α:25D - spirostane, needles, m.p. 166 to 170° C., $[\alpha]_D^{23} - 84°$ (*c*, 0.322).

The foregoing triol (2 g.) in pyridine (20 ml.) was oxidised with chromium trioxide (2 g.) in pyridine (20 ml.) for 24 hours at room temperature. The product was isolated with benzene and crystallised from acetone/hexane (1:4) to give 5:6ξ - *dihydroxy* - 6ξ - *methyl* - 5α:25D - *spirostan* - 3 - *one*, needles, m.p. 243 to 245° C., $[\alpha]_D^{23} - 75°$ (*c*, 0.292).

6ξ - *Hydroxy* - 6ξ - *methyl* - 25D - *spirost* - 4 - *en* - 3 - *one*. The foregoing diol (800 mg.) was heated under reflux in methanol (50 ml.) containing sodium hydroxide (400 mg.) for 1 hour. The product was isolated with ether and crystallised from acetone/hexane to give 6ξ - *hydroxy* - 6ξ - *methyl* - 25D - *spirost* - 4 - *en* - 3 - *one*, needles, m.p. 233 to 235° C., $[\alpha]_D^{23} - 52°$ (*c*, 0.73 in chloroform) $\lambda_{max.}$ 239 mμ (ε = 13,730).

6ξ - Hydroxy - 6ξ - methyl - 25D - spirost - 4 - en - 3 - one (100 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (100 mg.) in dry benzene (4 ml.) were heated under reflux for 21 hours and the product was isolated as in Example 1. 6ξ - *Hydroxy* - 6ξ - *methyl* - 25D - *spirosta* - 1:4 - *dien* - 3 - *one* crystallised from acetone/hexane (1:4) in needles, m.p. 248 to 250° C., λ_{max} 243 mμ (13,965) in ethanol, $\nu_{max.}$ 3410, 1670, 1620 and 1595 cm.$^{-1}$ in "Nujol" $[\alpha]_D^{22} - 118°$ (*c*, 0.06 in chloroform).

Example 37

9α - *Fluoro* - 11β:17β - *dihydroxy* - 6α:17α - *dimethylandrosta* - 1:4 - *dien* - 3 - *one*

9α - Fluoro - 11β:17β - dihydroxy - 6α:17α - dimethylandrost - 4 - ene - 3 - one (100 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (90 mg.) in dry benzene (4 ml.) and dioxan (3 ml.) were heated under reflux for 20 hours and the product was isolated as in Example 1. 9α - *Fluoro* - 11β:17β - *dihydroxy* - 6α:17α - *dimethylandrosta* - 1:4 - *dien* - 3 - *one* was obtained, $\lambda_{max.}$ 239 mμ (12,600) in ethanol, ν_{max} 3360, 1662, 1621 and 1600 cm^{-1} in "Nujol".

Example 38

11α - *Hydroxy* - 6α - *methylpregna* - 1:4 - *diene* - 3:20 - *dione*

11α - Hydroxy - 6α - methylpregn - 4 - ene - 3:20 - dione (40 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (35 mg.) in dry benzene (2 ml.) were heated under reflux for 20 hours, and the product was isolated as in Example 1, giving 11α - *hydroxy* - 6α - *methylpregna* - 1:4 - *diene* - 3:20 - *dione*, $\lambda_{max.}$ 244 mμ (15,130) in ethanol.

Example 39

6α - *Methyl* - 16α:17α - *isopropylidenedioxypregna* - 1:4 - *diene* - 3:20 - *dione*

6α - Methyl - 16α:17α - *iso*propylidenedioxypregn - 4 - ene - 3:20 - dione was prepared as follows:

A solution of potassium permanganate (3 g.) in a mixture of acetone (130 ml.) and water (25 ml.) was added during 20 minutes to a stirred solution of 6α - methylpregna - 4:16 - diene - 3:20 - dione (5.2 g.) in a mixture of acetone (160 ml.) and acetic acid (1.4 ml.). After treatment with sulphur dioxide, the pale yellow solution was decanted from inorganic salts, diluted with water, and the product extracted with ether. The extract was washed with aqueous sodium bicarbonate, water, and then dried. Concentration to 30 ml. gave crystals which were purified from aqueous ethanol. 16α:17α - *Dihydroxy* - 6α - *methylpregn* - 4 - *ene* - 3:20 - *dione* separated in needles, m.p. 223° to 225° C. $[\alpha]_D^{21} + 82°$ (*c*, 0.94 in chloroform), $\lambda_{max.}$ 240 mμ (log ε 4.19).

A suspension of the foregoing compound (200 mg.) in acetone (15 ml.) was treated with 1 drop of perchloric acid (72%). After 30 minutes, the mixture was poured into water and the product collected and purified from aqueous ethanol. 6α - Methyl - 16α:17α - *iso*propylidenedioxypregn - 4 - ene - 3:20 - dione formed needles, m.p. 167° C., $[\alpha]_D^{23} + 113°$ (*c*, 0.35 in chloroform), λ_{max} 240 mμ (log ε 4.17).

6α - Methyl - 16α:17α - *iso*propylidenedioxypregn - 4 - ene - 3:20 - dione (40 mg.) reacted with 2:3 - dichloro - 5:6 - dicyanobenzoquinone by the process of Example 38, gave 6α - *methyl* - 16α:17α - *isopropylidenedioxypregna* - 1:4 - *diene* - 3:20 - *dione*, $\lambda_{max.}$ 244 mμ (ε = 13,900) in ethanol, $\nu_{max.}$ 1712, 1665, 1621 and 1600 cm.$^{-1}$ in "Nujol".

EXAMPLE 40

20β - Hydroxy - 6α - methylpregna - 1:4 - dien - 3 - one

To a solution of 6α - methylpregn - 4 - ene - 3β:20β - diol (1 g.) in dry dioxan (5 ml.) was added a solution of 2:3 - dichloro - 5:6 - dicyano - 1:4 - benzoquinone (0.8 g.) in dry dioxan (5 ml.) and the mixture was kept at room temperature for 16 hours. The product was isolated as described in Example 1 and crystallised from aqueous methanol to give *20β - hydroxy - 6α - methylpregn - 4 - en - 3 - one* as needles, m.p. 170 to 171° C., $[\alpha]_D^{15}$ (EtOH) +72° (*c*, 0.9 in chloroform), $\lambda_{max.}$ 242.5 mμ (log ε 4.20).

20β Hydroxy - 6α - methylpregn - 4 - en - 3 - one (200 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (200 mg.) in dry benzene (4 ml.) were heated under reflux for 30 hours, and the product was isolated as in Example 1 to give *20β - hydroxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione* prisms, $\nu_{max.}$ 3480, 1650, 1610, 1590 and 1400 cm.$^{-1}$ in "Nujol", $\lambda_{max.}$ 244 mμ (14,240) in ethanol.

EXAMPLE 41

20:20 - Bisethylenedioxy - 6α - methylpregna - 1:4 - dien - 3 - one

20:20 - Bisethylenedioxy - 6α - methylpregn - 4 - en - 3 - one was prepared as follows:—

3β - Hydroxy - 6 - methylpregn - 5 - en - 20 - one (20 g.) was converted into its 20:20 - bisethylenedioxy derivative by treatment with ethylene glycol (250 ml.) and toluene - *p* - sulphonic acid (1 g.) at 80° C., with slow distillation *in vacuo* to remove water, for 5 hours, followed by precipitation into water and purification from methanol.

Oppenauer oxidation of the product (10 g.) with cyclohexanone (60 ml.) and aluminium *tert.*-butoxide (10 g.) in toluene (220 ml.) under reflux for 45 minutes gave 20:20 - *bisethylenedioxy - 6α - methylpregn - 4 - en - 3 - one*, $\lambda_{max.}$ 240.5 mμ (15,650) in ethanol.

20:20 - Bisethylenedioxy - 6α - methylpregn - 4 - en - 3 - one (200 mg.) treated by the process of Example 40 gave 20:20 - *bisethylenedioxy - 6α - methylpregna - 1:4 - dien - 3 - one*, $\lambda_{max.}$ 244 mμ (14,200) in ethanol, $\nu_{max.}$ 1662, 1625, 1602 and 1400 cm.$^{-1}$ in "Nujol".

EXAMPLE 42

Ethyl - 6α - methyl - 3 - oxopregna - 1:4:17(20) - trien - 21 - oate

Ethyl 6α - methyl - 3 - oxopregna - 4:17(20) - dien - 21 - oate (200 mg.) reacted with 2:3 - dichloro - 5:6 - dicyanobenzoquinone by the process of Example 40 gave *ethyl 6α - methyl - 3 - oxopregna - 1:4:17(20) - trien - 21 - oate*, $\lambda_{max.}$ 228 mμ (22,740) in ethanol.

EXAMPLE 43

17β - Hydroxy - 6α - methyl - 17α - (prop - 1 - ynyl) - androsta - 1:4 - dien - 3 - one

17β - Hydroxy - 6α - methyl - 17α - (prop - 1 - ynyl) - androst - 4 - en - 3 - one (1 g.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (800 mg.) in dry benzene (12 ml.) were heated under reflux for 10 hours and the product was isolated as in Example 1. *17β - Hydroxy - 6α - methyl - 17α - (prop - 1 - ynyl) - androsta - 1:4 - dien - 3 - one* exhibited $\lambda_{max.}$ 243 mμ (14,700) in ethanol, $\nu_{max.}$ 3605, 2240, 1663, 1615 and 1605 cm.$^{-1}$ in chloroform.

EXAMPLE 44

11 - Oxo - 6α - methylpregna - 1:4 - diene - 3:20 - dione

6α - Methylpregn - 4 - ene - 3:11:20 - trione (40 mg.) reacted with 2:3 - dichloro - 5:6 - dicyanobenzoquinone by the process of Example 38 gave *11 - oxo - 6α - methylpregna - 1:4 - diene - 3:20 - dione*, $\lambda_{max.}$ 239 mμ (13,920) in ethanol.

EXAMPLE 45

17α - Acetoxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione

17α - Acetoxy - 6α - methylpregn - 4 - ene - 3:20 - dione (180 mg.) reacted with 2:3 - dichloro - 5:6 - dicyanobenzoquinone by the process of Example 1 gave *17α - acetoxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione*, $\lambda_{max.}$ 244 mμ (15,050) in ethanol.

EXAMPLE 46

17α - Hexamyloxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione

17α - Hexamyloxy - 6α - methylpregn - 4 - ene - 3:20 - dione (200 mg.) reacted with 2:3 - dichloro - 5:6 - dicyanobenzoquinone by the process of Example 1 gave *17α - hexamyloxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione*, $\lambda_{max.}$ 243.5 mμ (14,920) in ethanol. "Nujol" is a Registered Trade Mark.

WHAT WE CLAIM IS:—

1. A process for the preparation of 3 - oxo - $\Delta^{1:4}$ - 6 - methyl and 3 - oxo - $\Delta^{1:4:6}$ - 6 - methyl steroids which process comprises reacting the corresponding 3 - oxo - Δ^4 - 6 - methyl or 3 - oxo - $\Delta^{4:6}$ - 6 - methyl steroid with 2:3 - dicyano - *p* - benzoquinone, which may be additionally substituted with one or two chlorine atoms, in a solvent.

2. A process as claimed in claim 1 wherein the corresponding 3 - oxo - Δ^4 - 6 - methyl or 3 - oxo - $\Delta^{4:6}$ - 6 - methyl steroids are reacted with 2:3 - dicyano - 5:6 - dichloro - 1:4 - benzoquinone.

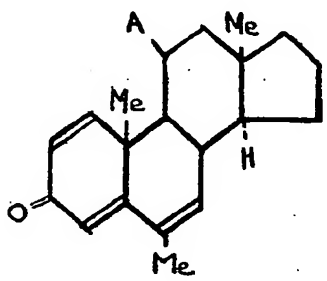
3. A process as claimed in either of the preceding claims wherein the solvent is benzene, dioxan, propyl acetate or acetic acid.

4. A process as claimed in claim 1 wherein the reaction is carried out at a temperature between 80° C. and 110° C.

5. A process as claimed in any one of the preceding claims wherein the reaction is car-

ried out in the presence of a catalytic quantity of *p* - nitrophenol.

6. 3 - Oxo - $\Delta^{1:4:6}$ - 6 - methyl steroids having, apart from substituents at the 16- and 17-positions, the general formula



where A is hydrogen or a keto or hydroxyl group.

7. 6α - Methylcholesta - 1:4 - dien - 3 - one.

8. 6 - Methylcholesta - 1:4:6 - trien - 3 - one.

9. 6α - Methyl - 25D - spirosta - 1:4 - dien - 3 - one.

10. 6 - Methyl - 25D - spirosta - 1:4:6 - trien - 3 - one.

11. 6ξ - Hydroxy - 6ξ - methyl - 25D - spirosta - 1:4 - dien - 3 - one.

12. 17β - Hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one.

13. 17β - Hydroxy - 6β - methylandrosta - 1:4 - dien - 3 - one.

14. 17β - Hydroxy - 6 - methylandrosta - 1:4:6 - trien - 3 - one.

15. 6α - Methylandrosta - 1:4 - diene - 3:17 - dione.

16. 6β - Methylandrosta - 1:4 - diene - 3:17 - dione.

17. 6 - Methylandrosta - 1:4:6 - triene - 3:17 - dione.

18. 17β - Hydroxy - 6α:17α - dimethylandrosta - 1:4 - dien - 3 - one.

19. 17β - Hydroxy - 6β:17α - dimethylandrosta - 1:4 - dien - 3 - one.

20. 17β - Hydroxy - 6:17α - dimethylandrosta - 1:4:6 - trien - 3 - one.

21. 17α - Ethynyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one.

22. 17α - Ethyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one.

23. 17α - Vinyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one.

24. 17α - (But - 1 - ynyl) - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one.

25. 17α - Ethynyl - 17β - hydroxy - 6 - methylandrosta - 1:4:6 - trien - 3 - one.

26. 17β - Acetoxy - 4:6α - dimethylandrosta - 1:4 - dien - 3 - one.

27. 17β - Acetoxy - 2:6α - dimethylandrosta - 1:4 - dien - 3 - one.

28. 9α - Fluoro - 11β:17β - dihydroxy - 6α:17α - dimethylandrosta - 1:4 - dien - 3 - one.

29. 17β - Hydroxy - 6α - methyl - 17α - (prop - 1 - ynyl) - androsta - 1:4 - dien - 3 - one.

30. 6α - Methylpregna - 1:4 - diene - 3:20 - dione.

31. 6 - Methylpregna - 1:4:6 - triene - 3:20 - dione.

32. 17α - Hydroxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione.

33. 17α - Hexamoyloxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione.

34. 11α - Hydroxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione.

35. 11 - Oxo - 6α - methylpregna - 1:4 - diene - 3:20 - dione.

36. 6α:16α - Dimethylpregna - 1:4 - diene - 3:20 - dione.

37. 6α - Methylpregna - 1:4:16 - triene - 3:20 - dione.

38. 6α - Methyl - 16α:17α - *iso*propylidenedioxypregna - 1:4 - diene - 3:20 - dione.

39. 20β - Hydroxy - 6α - methylpregna - 1:4 - dien - 3 - one.

40. 20:20 - Bisethylenedioxy - 6α - methylpregna - 1:4 - dien - 3 - one.

41. Ethyl 6α - methyl - 3 - oxopregna - 1:4:17(20) - trien - 21 - oate.

42. 17α - Acetoxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione.

43. A process for the preparation of 3 - oxo - $\Delta^{1:4}$ - 6 - methyl and 3 - oxo - $\Delta^{1:4:6}$ - 6 - methyl steroids substantially as described with reference to any one of the specific examples hereinbefore set forth.

A. G. R. CLARKE,
Agent for the Applicants.

PROVISIONAL SPECIFICATION

Improvements in or relating to 6-Methyl Steroid Compounds

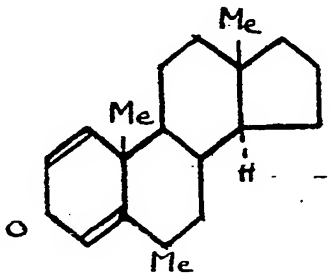
We, THE BRITISH DRUG HOUSES LIMITED, a British Company, of 16—34 Graham Street, City Road, London, N.1, do hereby declare this invention to be described in the following statement:—

This invention is for improvements in or relating to organic compounds and has particular reference to the 1-dehydro derivatives of certain unsaturated steroidal 6-methyl-3-ones.

In our copending Applications Nos. 17799/55 (No. 802,004), 18118/55 (No. 802,005), 9378/56 (No. 809,465), 26161/57 (No. 843,353) and 30878/57 (No. 852,683) methods are described for the preparation of 3 - oxo - Δ^4- and 3 - oxo - $\Delta^{4:6}$ - 6 - methyl steroidal hormones which compounds often possess more potent biological properties than their corresponding 6 - desmethyl analogues.

It is an object of the present invention to provide a process for the conversion of 3 - oxo - Δ^4 - 6 - methyl and 3 - oxo - $\Delta^{1:6}$ - 6 - methyl steroidal derivatives into the corresponding 1 - dehydro - derivatives which are a new class of compounds often possessing high biological activity.

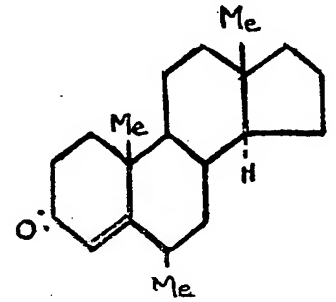
The present invention provides new 1 - dehydro - derivatives of 3 - oxo - $\Delta^{1:6}$ - 6 - methyl and certain 3 - oxo - Δ^4 - 6 - methyl steroids having the formula



(I)

(with or without a double bond at the 6:7 position) which 1 - dehydro - derivatives are of value on account of their biological properties or as intermediates in the preparation of compounds with useful biological properties as herein indicated or as is apparent to those skilled in the art.

According to the present invention there is provided a process for the preparation of 3 - oxo - $\Delta^{1:4}$ - 6 - methyl and 3 - oxo - $\Delta^{1:4:6}$ - 6 - methyl steroids which process comprises treating the corresponding 3 - oxo - Δ^4 - 6 - methyl or 3 - oxo - $\Delta^{4:6}$ - 6 - methyl steroids having the formula



(II)

(with or without a double bond at the 6:7 position) with 2:3 - dicyano - *p* - benzoquinone which may be additionally substituted with one or two chlorine atoms, in a solvent. Preferably 2:3 - dicyano - 5:6 - dichloro - 1:4 - benzoquinone is employed.

The choice of solvent is not critical providing both the steroid and quinone are soluble and stable therein. Benzene, dioxan, propyl acetate and acetic acid are preferred. Other solvents that may be employed include chlorobenzene, diethyleneglycol diethyl ether, phenetole, dimethylformamide or nitrobenzene. The dehydrogenation is preferably performed at an elevated temperature and conveniently between 80° C. and 110° C. Theoretically the reaction is best performed under nitrogen, but this precaution has little practical significance in the majority of cases herein. The rate of dehydrogenation may be increased by addition of a catalytic quantity of a proton donor and in particular by the addition of a catalytic quantity of *p* - nitrophenol. Completion of the reaction is generally indicated by discharge of the colour of the quinone and/or by the fact that further quantities of the hydroquinone derivatives are no longer deposited from the hot reaction liquors. Alternatively, completion of the reaction may be determined by estimating the quantity of quinone present in the reaction liquors by standard methods well known to those skilled in the art.

The 1 - dehydro - steroidal derivative is isolated from the reaction liquors by any convenient procedure. Thus the reaction liquors may be filtered to remove the sparingly soluble hydroquinone, extracted with aqueous alkali to remove phenolic products, evaporated to dryness, under reduced pressure if desired, and the residual solids crystallised in the usual way. Other methods will be apparent to those skilled in the art.

The process of the invention is of wide applicability and may, in general, be applied to 3 - oxo - Δ^4 - 6 - methyl and 3 - oxo - $\Delta^{1:6}$ - 6 - methyl derivatives of androstane, pregnane, cholestane and spirostane, additionally substituted by such groups as oxo (including 20 - oxo - 16 - ene), hydroxy, alkoxy, acyloxy, fluoro, alkyl and ethinyl.

The invention also provides the following new steroidal 6 - methyl - 1:4 - dien - 3 - ones and 6 - methyl - 1:4:6 - trien - 3 - ones which are of value in steroid technology, in the furtherance of steroidal research and in the application of steroidal materials to veterinary or medical practice, whether as tablets, elixirs, injections, implants, or other types of pharmaceutical preparation well known to those skilled in the art.

Cholestane series

6α - Methylcholesta - 1:4 - dien - 3 - one and 6 - methylcholesta - 1:4:6 - trien - 3 - one which are of value as tools in the study of the regulation of blood cholesterol levels.

Spirostane series

6α - Methyl - 25D - spirosta - 1:4 - dien - 3 - one and 6 - methyl - 25D - spirosta - 1:4:6 - trien - 3 - one which are of value as intermediates in the preparation of 6 - methylated aromatic steroid hormones.

Androstane series

17β - Hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one

17β - Hydroxy - 6β - methylandrosta - 1:4 - dien - 3 - one

17β - Hydroxy - 6 - methylandrosta - 1:4:6 - trien - 3 - one

6α - Methylandrosta - 1:4 - diene - 3:17 - dione
6β - Methylandrosta - 1:4 - diene - 3:17 - dione
6 - Methylandrosta - 1:4:6 - triene - 3:17 - dione
17β - Hydroxy - 6α:17α - dimethylandrosta - 1:4 - dien - 3 - one
17β - Hydroxy - 6β:17α - dimethylandrosta - 1:4 - dien - 3 - one
17β - Hydroxy - 6:17α - dimethylandrosta - 1:4:6 - trien - 3 - one
17α - Ethinyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one
17α - Ethyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one
17α - Vinyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one
17α - (But - 1 - ynyl) - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one
17α - Ethinyl - 17β - hydroxy - 6 - methylandrosta - 1:4:6 - trien - 3 - one

which are of value as intermediates in the preparation of 6-methylated aromatic steroidal hormones, as intermediates in the preparation of biologically active compounds and in some cases on account of their biological properties.

Pregnane series

6α - Methylpregna - 1:4 - diene - 3:20 - dione
6 - Methylpregna - 1:4:6 - triene - 3:20 - dione
17α - Hydroxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione
17α - Caproyloxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione
11α - Hydroxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione
11 - Oxo - 6α - methylpregna - 1:4 - diene - 3:20 - dione
6α:16α - Dimethylpregna - 1:4 - diene - 3:20 - dione
21 - Fluoro - 6α - methylpregna - 1:4 - diene - 3:20 - dione
17α:21 - Dihydroxy - 6α - methylpregna - 1:4 - diene - 3:11:20 - trione and its acetate
11β:17α:21 - Trihydroxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione and its acetate
6α - Methylpregna - 1:4:16 - triene - 3:20 - dione

which are of value as intermediates in the preparation of compounds with valuable biological properties such as progestational properties or properties associated with the adreno-cortical hormones or as intermediates in the preparation of compounds with useful biological properties. Thus, for example, 17α:21 - dihydroxy - 6α - methylpregna - 1:4 - diene - 3:11:20 - trione and its acetate and 11β:17α:21 - trihydroxy - 6α - methylpregna - 1:4 - diene - 3:20 - trione and its acetate are of value on account of their hydrocortisone-like anti-inflammatory properties.

Following is a description by way of example of methods of carrying the invention into effect.

EXAMPLE 1

6α - *Methylpregna* - 1:4 - *diene* - 3:20 - *dione*

6α - Methylprogesterone (650 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (500 mg.) in dry benzene (30 ml.) were boiled under reflux for 12 hours. The solids were removed by filtration, and the filtrate diluted with ether and washed with 4% aqueous sodium hydroxide, then with water, dried (Na_2SO_4), stirred with decolourising charcoal, filtered and the solvent evaporated. Crystallisation from hexane gave 6α - *methylpregna* - 1:4 - *diene* - 3:20 - *dione*, prisms, m.p. 140 to 141° C., $[\alpha]_D^{22} + 110°$ (*c*, 0.22 in chloroform); $\lambda_{max.}$ 245 mμ (15,400) in ethanol $\lambda_{max.}$ 1697, 1655, 1616, 1602 cm.$^{-1}$ (in chloroform).

EXAMPLE 2

6 - *Methylpregna* - 1:4:6 - *triene* - 3:20 - *dione*

6 - Methylpregna - 4:6 - diene - 3:20 - dione (200 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (200 mg.) in dry benzene (10 ml.) were heated under reflux for 7 hours. The product was isolated as in the previous example. 6 - *Methylpregna* - 1:4:6 - *triene* - 3:20 - *dione* separated from acetone/hexane (1:6) in rods, m.p. 168° C., $[\alpha]_D +$ 100° (*c*, 0.25 in chloroform) $\lambda_{max.}$ 228 mμ (12,240), 303 mμ (10,860) $\lambda_{inflex.}$ 251 mμ (8,280) in ethanol.

EXAMPLE 3

6 - *Methylandrosta* - 1:4:6 - *triene* - 3:17 - *dione*

6 - Methylandrosta - 4:6 - dione - 3:17 - dione (60 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (50 mg.) in dry benzene (4 ml.) were heated under reflux for 12 hours, then the product was isolated as in previous examples. 6 - Methylandrosta - 1:4:6 - triene - 3:17 - dione formed prisms, [from acetone/hexane, (1:5)] m.p. 219 to 221° C., $[\alpha]_D^{22} + 84°$ (*c*, 0.21 in chloroform), $\lambda_{max.}$ 227 mμ (12,720), 301 mμ (11,720) $\lambda_{inflex.}$ 250 mμ (9,050) in ethanol.

EXAMPLE 4

17β - *Hydroxy* - 6α - *methylandrosta* - 1:4 - *dien* - 3 - *one*

6α - Methyltestosterone (120 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (120 mg.) in dry benzene (6 ml.) were heated under reflux for 16 hours, and the product isolated as in previous examples. 17β - Hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one separated from ether/hexane (1:4) in prisms, m.p. 136 to 139° C., $[\alpha]_D^{21} + 2°$ (*c*., 0.09 in chloroform), $\lambda_{max.}$ 244 mμ (13,270) in ethanol.

EXAMPLE 5

17β - Hydroxy - 6β - methylandrosta - 1:4 - diene - 3 - one

6β - Methyltestosterone, treated as described for the 6α - methyl isomer, gave *17β - hydroxy - 6β - methylandrosta - 1:4 - dien - 4 - one*, prisms from ether, m.p. 188 to 190° C., $\lambda_{max.}$ 245 mμ (14,070) in ethanol.

EXAMPLE 6

17β - Hydroxy - 6β:17α - dimethylandrosta - 1:4 - dien - 3 - one

6β:17α - Dimethyltestosterone (100 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (100 mg.) in dry benzene (4 ml.) were heated under reflux for 7 hours, when the product was isolated as in previous examples. *17β - Hydroxy - 6β:17α - dihydroxyandrosta - 1:4 - dien - 3 - one* separated from ether/hexane (1:6) in needles, $[\alpha]_D^{24}$ —17° (*c*, 0.23 in chloroform), m.p. 118 to 120° C., $\lambda_{max.}$ 245 mμ (14.480).

EXAMPLE 7

Purified dioxan (5 ml.) was substituted for benzene in the previous Example, with similar results.

EXAMPLE 8

n-Propyl acetate (5 ml.) was substituted for benzene in Example 1 with similar results.

EXAMPLE 9

Acetic acid (5 ml.) was substituted for benzene in Example 1 with similar results.

EXAMPLE 10

6α - Methylpregna - 1:4 - diene - 3:20 - dione

6α - Methylprogesterone (100 mg.), 2:3 - dichloro - 5:6 - dicyanobenzoquinone (90 mg.) and *p* - nitrophenol (10 mg.) in dry benzene were heated under reflux for 6 hours and the product isolated as in Example 1. 6α - Methylpregna - 1:4 - diene - 3:20 - dione was obtained, m.p. and mixed m.p. 139 to 141° C. with the sample obtained in Example 1, $\lambda_{max.}$ 245 mμ (15,450) in ethanol.

EXAMPLE 11

2:3 - Dicyanobenzoquinone was substituted for the dichlorodicyanobenzoquinone in the previous example, and the mixture heated under reflux for 24 hours. *6α - Methylpregna - 1:4 - diene - 3:20 - dione*, m.p. 139 to 140° C., $\lambda_{max.}$ 245 mμ (15,320) in ethanol was obtained.

EXAMPLE 12

17α - Hydroxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione

17α - Hydroxy - 6α - methylprogesterone (200 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (200 mg.) in dry benzene (4 ml.) were heated under reflux for 7 hours, and the product isolated as in Example 1. *17α - Hydroxy - 6α - methylpregna - 1:4 - diene - 3:20 - dione* separated from acetone/hexane (1:4) in prisms, m.p. 235 to 237° C., $[\alpha]_D^{18}$ + 12° (*c*, 0.29 in chloroform), $\lambda_{max.}$ 244.5 mμ (14,700) in ethanol.

EXAMPLE 13

6α:16α - Dimethylpregna - 1:4 - diene - 3:20 - dione

6α:16α - Dimethylprogesterone (100 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (80 mg.) in dry benzene (8 ml.) were heated under reflux for 22 hours and the product isolated as in Example 1. *6α:16α - Dimethylpregna - 1:4 - diene - 3:20 - dione* crystallised from acetone/hexane (1:3) in prisms, m.p. 132 to 134° C., $\lambda_{max.}$ 245 mμ (13,900) in ethanol.

EXAMPLE 14

6α - Methylcholesta - 1:4 - dien - 3 - one

6α - Methylcholest - 4 - en - 3 - one (150 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (120 mg.) in dry benzene (8 ml.) were heated under reflux for 18 hours, then the product was isolated as in Example 1. *6α - Methylcholesta - 1:4 - dien - 3 - one* was obtained as a gum, $[\alpha]_D^{20}$ + 21° (*c*, 0.15 in chloroform) $\lambda_{max.}$ 245 mμ (13,700) in ethanol.

EXAMPLE 15

6 - Methylcholesta - 1:4:6 - trien - 3 - one

6 - Methylcholesta - 4:6 - dien - 3 - one (250 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (200 mg.) in dry benzene (20 ml.) were heated under reflux for 10½ hours, then the product was isolated as in Example 1. *6 - Methylcholesta - 1:4:6 - trien - 3 - one* crystallised from aqueous ethanol in prisms, m.p. 80 to 81° C. $\lambda_{max.}$ 229 mμ (11,440), 303 mμ (9,290) $\lambda_{inflex.}$ 250 mμ (8,460).

EXAMPLE 16

6α - Methyl - 25D - spirosta - 1:4 - dien - 3 - one

6α - Methyl - 25D - spirost - 4 - en - 3 - one (50 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (45 mg.) in dry benzene (4 ml.) were heated under reflux for 35 hours, and the product isolated as in Example 1. *6α - Methyl - 25D - spirosta - 1:4 - dien - 3 - one* separated from methylene chloride/methanol (1:4) in needles, m.p. 237 to 239° C., $\lambda_{max.}$ 244 mμ (15,330), $[\alpha]_D^{20}$ – 34° (*c*, 0.19 in chloroform).

EXAMPLE 17

6 - Methyl - 25D - spirosta - 1:4:6 - trien - 3 - one

6 - Methyl - 25D - spirosta - 4:6 - dien - 3 - one (210 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (160 mg.) in dry benzene (20 ml.) were heated under reflux for 11 hours, then the product was isolated as in Example 1. *6 - Methyl - 25D - spirosta - 1:4:6 - trien - 3 - one* formed needles from methylene chloride/methanol (1:3), m.p. 253 to 255° C., $\lambda_{max.}$ 228 mμ (13,110), 303 mμ (11,252), $\lambda_{inflex.}$ 250 mμ (9,260).

EXAMPLE 18

17β - Hydroxy - 6 - methylandrosta - 1:4:6 - trien - 3 - one

17β - Hydroxy - 6 - methylandrosta - 4:6 - dien - 3 - one (100 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (85 mg.) in dry benzene (4 ml.) were heated under reflux for 13 hours, then the product was isolated as in Example 1. *17β - Hydroxy - 6 - methylandrosta - 1:4:6 - trien - 3 - one* separated from ether/hexane (1:4) in prisms, m.p. 169 to 170° C., $\lambda_{max.}$ 228 mμ (11,470), 251 mμ (8,020), 302.5 mμ (10,520).

EXAMPLE 19

6α - Methylandrosta - 1:4 - diene - 3:17 - dione

6α - Methylandrost - 4 - ene - 3:17 - dione (120 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (100 mg.) in dry benzene (10 ml.) were heated under reflux for 24 hours, then the product was isolated as in Example 1. *6α - Methylandrosta - 1:4 - diene - 3:17 - dione* separated from acetone/hexane (1:6) in prisms, m.p. 210 to 212° C., $\lambda_{max.}$ 243 mμ (14,540), $[\alpha]_D^{20}$ + 103 (*c*, 0.28 in chloroform).

EXAMPLE 20

6β - Methylandrosta - 1:4 - dien - 3:17 - dione

6β - Methylandrost - 4 - ene - 3:17 - dione (80 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (70 mg.) in dry benzene (7 ml.) were heated under reflux for 13 hours, then the product was isolated as in Example 1. *6β - Methylandrost - 4 - ene - 3:17 - dione* crystallised from ether/hexane (1:5) in needles, m.p. 176 to 178° C., $\lambda_{max.}$ 243 mμ (14,000), $[\alpha]_D^{20}$ + 102 (*c*, 0.19 in chloroform).

EXAMPLE 21

2:3 - Dicyanobenzoquinone (50 mg.) was substituted for the dichloro - dicyanobenzoquinone in Example 3, and heating was continued for 20 hours with similar results.

EXAMPLE 22

17β - Hydroxy - 6α:17α - Dimethylandrosta - 1:4 - dien - 3 - one

17β - Hydroxy - 6α:17α - dimethylandrost - 4 - en - 3 - one (60 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (50 mg.) in dry benzene (4 ml.) were heated under reflux for 10 hours, then the product was extracted as in Example 1. *17β - Hydroxy - 6α:17α - dimethylandrosta - 1:4 - dien - 3 - one* crystallised from ether/hexane (1:8) in rectangular prisms, m.p. 143 to 144° C., $\lambda_{max.}$ 244 mμ (14,080) in ethanol.

EXAMPLE 23

17β - Hydroxy - 6:17α - dimethylandrosta - 1:4:6 - trien - 3 - one

17β - Hydroxy - 6:17α - dimethylandrosta - 4:6 - dien - 3 - one (110 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (90 mg.) in dry benzene (10 ml.) were heated under reflux for 20 hours, and the product isolated as in Example 1. *17β - Hydroxy - 6:17α - dimethylandrosta - 1:4:6 - trien - 3 - one* separated from ether/hexane (1:3) in needles, m.p. 148 to 149° C., λ_{max} 229 mμ (12,780), 250 mμ (8,840), 303 mμ (11,215) in ethanol.

EXAMPLE 24

17α - Ethinyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one

6α - Methylethisterone (150 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (170 mg.) and *p* - nitrophenol (15 mg.) in dry benzene (8 ml.) were heated under reflux for 18 hours, and the product isolated as in Example 1. *17α - Ethinyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one* separated from ether/hexane (1:1) in prisms, m.p. 140 to 142° C., $\lambda_{max.}$ 244 mμ (13,730) in ethanol.

EXAMPLE 25

17α - Vinyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one

17α - Vinyl - 17β - hydroxy - 6α - methylandrost - 4 - en - 3 - one (0.5 g.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (0.5 g.) in dry benzene (10 ml.) were heated under reflux for 26 hours. *17α - Vinyl - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one*, isolated as in Example 1, crystallised from acetone/hexane (1:4) in prisms, m.p. 187 to 189° C., $[\alpha]_D^{20}$ + 3° (*c*, 0.18 in chloroform) $\lambda_{max.}$ 244.5 mμ (14,760) in ethanol.

EXAMPLE 26

17α - (But - 1 - ynyl) - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one

17α - (But - 1 - ynyl) - 17β - hydroxy - 6α - methylandrost - 4 - en - 3 - one (200 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (160 mg.) in dry benzene (15 ml.) were heated under reflux for 20 hours and the product isolated as in Example 1. *17α - (But - 1 - ynyl) - 17β - hydroxy - 6α - methylandrosta - 1:4 - dien - 3 - one* crystallised from ether/hexane (1:4) in needles, m.p. 133 to 136° C., $\lambda_{max.}$ 245 mμ (13,370) in ethanol.

EXAMPLE 27

17α:21 - Dihydroxy - 6α - methylpregna - 1:4 - diene - 3:11:20 - trione

6α - Methylcortisone (200 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (200 mg.) in purified dioxan (5 ml.) were heated under reflux until no further deposition of 2:3 - dichloro - 5:6 - dicyanohydroquinone (glistening plates) was observed (8 hours). The mixture was diluted with chloroform, the solids removed by filtration, and the solution washed with 5% sodium hydroxide solution saturated with sodium chloride until no more colour was removed in the aqueous phase. The chloroform was then washed with saturated sodium chloride solution, dried (Na_2SO_4) and evaporated. Purification from ethyl acetate/hexane (1:2) gave *17α:21 - dihydroxy - 6α - methylpregna - 1:4 - diene 3:11:20 - trione* in prisms, m.p. 231 to 234° C., $\lambda_{max.}$ 238.5 mμ (14,130) in ethanol.

EXAMPLE 28

21 - *Acetoxy* - 17α - *hydroxy* - 6α - *methylpregna* - 1:4 - *diene* - 3:11:20 - *trione*

6α - Methylcortisone acetate (60 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (50 mg.) in purified dioxan (3 ml.) were heated under reflux for 10 hours, and the product isolated as in Example 27. 21 - *Acetoxy* - 17α - *hydroxy* - 6α - *methylpregna* - 1:4 - *diene* - 3:11:20 - *trione* was identified by its ultra-violet absorption spectrum, ($\lambda_{max.}$ 238.5 mμ [ε=13,740] in ethanol) and infra-red absorption spectrum ($\lambda_{max.}$ 1664, 1622, 1603 $cm.^{-1}$ in chloroform).

EXAMPLE 29

11β:17α:21 - *Trihydroxy* - 6α - *methylpregna* - 1:4 - *diene* - 3:20 - *dione*

6α - Methyl - hydrocortisone (100 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (90 mg.) in anhydrous dioxan (5 ml.) were heated under reflux for 18 hours. Isolation as described under Example 27, and purification from aqueous acetone, gave 11β:17α:21 - *trihydroxy* - 6α - *methylpregna* - 1:4 - *diene* - 3:20 - *dione*, m.p. 204 to 208° C. $[\alpha]_D^{22}+98°$ (*c*, 0.21 in dioxan), $\lambda_{max.}$ 243 mμ (ε 14,600) (in ethanol).

EXAMPLE 30

21 - *Acetoxy* - 11β:17α - *dihydroxy* - 6α - *methylpregna* - 1:4 - *diene* - 3:20 - *dione*

21 - Acetoxy - 11β:17α - dihydroxy - 6α - methylpregn - 4 - ene - 3:20 - dione (60 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (50 mg.) were heated in purified dioxan (4 ml.) under reflux for 12 hours. The product, isolated as in Example 27 was purified from aqueous acetone to give 21 - *acetoxy* - 11β:17α - *dihydroxy* - 6α - *methylpregna* - 1:4 - *diene* - 3:20 - *dione*, m.p. 203 to 206° C., $[\alpha]_D^{22}+103°$ (*c*, 0.12 in dioxan), $\lambda_{max.}$ 243.5 mμ (ε=14,750) in ethanol.

EXAMPLE 31

17α - *Ethyl* - 17β - *hydroxy* - 6α - *methylandrosta* - 1:4 - *dien* - 3 - *one*

17α - Ethyl - 17β - hydroxy - 6α - methylandrost - 4 - en - 3 - one (270 mg). and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (270 mg.) and *p* - nitrophenol (30 mg.) in dry benzene (4 ml.) were heated under reflux for 8½ hours and the product isolated as in Example 1. 17α - *Ethyl* - 17β - *hydroxy* - 6α - *methylandrosta* - 1:4 - *dien* - 3 - *one* was obtained as a gum, $\lambda_{max.}$ 245 mμ (12,400) in ethanol.

EXAMPLE 32

6α - *Methylpregna* - 1:4:16 - *triene* - 3:20 - *dione*

6α - Methylpregna - 4:16 - diene - 3:20 - dione (150 mg.) 2:3 - dichloro - 5:6 - dicyanobenzoquinone (150 mg.) and *p* - nitrophenol (15 mg.) in dry benzene (5 ml.) were heated under reflux for 7 hours and the product isolated as in Example 1, and purified from ether/hexane (1:6). 6α - *Methylpregna* - 1:4:16 - *triene* - 3:20 - *dione* formed needles, m.p. 198 to 199° C., $\lambda_{max.}$ 241 mμ (22,710) in ethanol, $\lambda_{max.}$ 1657, 1616, 1600, 1586 $cm.^{-1}$ in chloroform.

EXAMPLE 33

17α - *Ethinyl* - 17β - *hydroxy* - 6 - *methylandrosta* - 1:4:6 - *trien* - 3 - *one*

17α - Ethinyl - 17β - hydroxy - 6 - methylandrosta - 4:6 - dien - 3 - one (m.p. 202 to 204° C.) (840 mg.) and 2:3 - dichloro - 5:6 - dicyanobenzoquinone (840 mg.) in dry benzene (12 ml.) were heated under reflux for 3 hours and the product isolated as in Example 1. 17α - *Ethinyl* - 17β - *hydroxy* - 6 - *methylandrosta* - 1:4:6 - *trien* - 3 - *one* crystallised from acetone/hexane (1:6) in prisms, m.p. 148 to 150° C., $\lambda_{max.}$ 228 mμ (12,680), 302.5 mμ (11.080), λ_{inflex} 250 mμ (8,760) in ethanol.

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